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Highlights of the ESPEN-ESPGHAN-ECFS Guidelines on Nutrition Care for Infants and Children With Cystic Fibrosis

*Michael Wilschanski, †Christian P. Braegger, ‡Carla Colombo, §Dimitri Declercq, ||Alison Morton, ¶Ruzha Pancheva, #Eddy Robberecht, **Martin Stern, ††Birgitta Strandvik, ‡‡Sue Wolfe, and §§Stephane M. Schneider

The European Society for Clinical Nutrition and Metabolism (ESPEN) launched a process of developing updated guidelines on nutrition care for infants, children, and adults with cystic fibrosis (CF). To that end, a group of experts systematically reviewed the medical literature to summarize current knowledge on epidemiology and pathophysiology, prevention, and treatment of CF-related undernutrition. The group included representatives from several European countries, physicians, dietitians, and educators, all experts in the field of CF, and the guidelines coordinator. The group recommended evidence-based guidelines on nutrition care for infants, children, and adults with CF. The experts followed the GRADE method, which was based on determinations of *grade of evidence* and *strength of recommendation*. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Cystic Fibrosis (ECFS), who are partners of these guidelines, reviewed the final manuscript, with an external review for ESPGHAN. The reader of the Journal is kindly invited to refer to the original article published in the June 2016 issue of *Clinical Nutrition* (1).

This summary will outline some of the recommendations on nutrition care for infants and children with CF.

From the *Department of Pediatric Gastroenterology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, the †Division of Gastroenterology and Nutrition and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland, the ‡Fondazione IRCC Ca' Granda, Ospedale Maggiore Policlinico (IRSS), Universita degli Studi di Milano, Milan, Italy, the §Department of Pediatrics, CF Center, Ghent University Hospital, Ghent, Belgium, the ||Regional Adult CF Unit, St James' University Hospital, Leeds, UK, the ¶Department of Hygiene, Faculty of Public Health, Prof Dr Paraskev Stoyanov Medical University of Varna, Varna, Bulgaria, the #Department of Pediatric Gastroenterology, Hepatology and Nutrition, University of Ghent, CF Center, Princess Elizabeth Pediatric Hospital, Ghent, Belgium, the **University Children's Hospital, University of Tubingen, Tubingen, Germany, the ††Department of Bioscience and Nutrition, Karolinska Institute, Novum, Stockholm, Sweden, the ‡‡Regional Pediatric CF Unit, The Leeds Children's Hospital, Leeds, UK, and the §§Gastroenterology and Clinical Nutrition, Archet University Hospital and University of Nice Sophia-Antipolis, Nice, France.

Address correspondence and reprint requests to Michael Wilschanski, MBBS, Department of Pediatric Gastroenterology, Hadassah-Hebrew University Medical Center, PO Box 24035, Jerusalem, Israel (e-mail: michaelwil@hadassah.org.il).

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SCOPE OF THE PROBLEM

CF is a life-threatening autosomal recessive genetic disease, caused by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The incidence in Caucasians is 1 in 3500 births. Defective or absent CFTR function alters Na^+ and Cl^- transport across excretory epithelia, which contributes to both the morbidity and mortality of the disease. CF prognosis is strongly associated with poor nutritional status. Although the nutritional status of people with CF has improved markedly over the past 2 decades, adequate nutrition still remains a major problem for some. Indeed, according to the most recent ECFS Patient Registry data, half of people with CF in Europe do not achieve adequate nutritional status. People with CF who are diagnosed early through newborn screening programs benefit from earlier intervention. This gives the opportunity to minimize nutritional deficits and is associated with positive nutritional outcomes. To achieve the best possible outcome for each person with CF, it is important to provide care that includes attention to nutrition.

CAUSES OF UNDERNUTRITION IN CYSTIC FIBROSIS

Undernutrition in CF results from a combination of conditions—energy losses, high-energy needs, and inadequate nutrient intake. The primary cause of energy loss is malabsorption, often resulting from maldigestion due to insufficient release of pancreatic enzymes into the intestinal lumen (exocrine pancreatic insufficiency). Energy losses are further worsened when digestive abnormalities are associated with metabolic changes, for example, intestinal inflammation, small intestinal bacterial overgrowth, low bicarbonate output, impaired insulin secretion with a variable degree of insulin resistance (CF-related diabetes), and impaired liver function (CF-related liver disease).

Furthermore, energy needs are higher in people with CF and pancreatic insufficiency in comparison with needs of healthy individuals, an observation supported by measurement of high resting energy expenditure in people with CF. Such high-energy expenditure correlates strongly with pancreatic insufficiency, although the mechanism remains unclear. Furthermore, high-energy requirements have also been attributed to persistent lung inflammation and infections associated with CF.

People with CF may be unable to consume sufficient energy to overcome shortfalls due to inefficient energy use and increased energy needs. Psychosocial issues, such as stress and treatment noncompliance, may contribute to energy shortfalls. Pulmonary inflammation, discomforts related to associated gastrointestinal problems (gastroesophageal reflux, constipation, distal intestinal

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obstructive syndrome, bacterial overgrowth), and the adverse effects of medications can also decrease appetite and interfere with intake goals.

CONSEQUENCES OF UNDERNUTRITION IN CYSTIC FIBROSIS

Undernutrition affects respiratory muscle function, decreases exercise tolerance, and leads to immunological impairment. Although CF pathophysiology is directly linked to a deficit of energy intake relative to needs, CF also affects multiple body systems in ways that further worsen pulmonary status, impair growth, lower quality of life, and shorten life expectancy.

In infants and young children with CF, poor nutritional status results in stunted growth, as detected by low weight- and height-for-age percentiles. If untreated, such CF-related undernutrition in infancy or early childhood can lead to the serious consequence of impaired cognitive function. In cases of severe undernutrition in infants and children, lung function worsens markedly, and survival is poor.

As CF progresses in older children, a wide range of metabolic complications cause nutritional deficits, which further compromise quality of life and increase mortality risk. For example, CF-related diabetes—insulin deficiency and/or insulin resistance—causes and worsens malnutrition by lowering insulin's anabolic effects. Similarly, CF-related liver disease and hepatic steatosis are associated with selective nutritional deficiencies, for example, fat-soluble vitamins, essential fatty acids, and calcium, this in turn worsening malnutrition and contributing to problems such as reduced bone mineral density.

Taken together, such adverse consequences of nutrient deficits in infants and children with CF are a rationale for early and aggressive nutrition intervention, beginning in the first years of life and continuing over the lifespan of the patient.

A SYSTEMATIC APPROACH TO NUTRITIONAL ASSESSMENT AND MONITORING IN CYSTIC FIBROSIS

At all ages, individuals with CF are at nutritional risk; therefore, routine and complete nutritional assessments are essential to improve outcomes. For infants who are diagnosed by newborn screening, attention to nutrition is key to maintaining normal growth—even before signs of the CF phenotype become evident.

Criteria indicating adequate nutritional status are described in Table 1; recommendations for nutritional assessment and follow-up, and for energy requirements are shown in Tables 2 and 3, respectively.

TABLE 1. Criteria indicating adequate nutritional status

Infants and children ≤2 years: 0 SD (50th percentile) of weight and length for a healthy same-age population.
Children 2–18 years: 0 SD (50th percentile) of BMI for a healthy, same-age population. Change in height percentile/SD score should be considered, as stunted children can have a normal BMI. Any height measurement should be interpreted taking parental height into consideration.
Lean body mass and bone mineral content are more sensitive indicators of nutritional deficit than low BMI; low values predict impaired lung function in children with CF.

BMI = body mass index; CF = cystic fibrosis; SD = standard deviation.

PANCREATIC ENZYME REPLACEMENT THERAPY

Pancreatic enzyme replacement therapy (PERT) is vital to maintain adequate nutritional status in people with CF with exocrine pancreatic insufficiency; the efficacy of this treatment is well established. Recommendations for PERT are described in Table 4.

FEEDING INFANTS AND CHILDREN WITH CYSTIC FIBROSIS

Exclusive breast-feeding is recommended for newly diagnosed infants with CF, and the use of a regular infant formula if breastfeeding is not possible (grade of evidence: *low*).

Dietary counseling is essential throughout early childhood when long-term feeding habits are being established. Advice from a CF dietitian should be tailored to the individuals' age and evolving independence, clinical status, and support the goal of self-care.

Nutrition education and behavioral counseling are recommended for all families of infants and children with CF (grade of evidence: *high*).

TABLE 2. Recommendations for nutritional assessment and follow-up

For pancreatic-sufficient infants and children, it is suggested that an annual assessment of pancreatic function by fecal pancreatic elastase-1 determination, with the test repeated when inadequate growth and/or nutritional status occur(s).
For children and adolescents, it is recommend assessing for pancreatic enzyme replacement therapy (PERT) need or adequacy of treatment by monitoring growth, nutritional status, and gastrointestinal symptoms; monitoring is suggested every month for children, and every 3 months for adolescents (grade of evidence: *low*).
For children, care managers are suggested to consider annual nutritional review with blood tests (blood count, iron status, plasma fat-soluble vitamin levels, serum liver function tests, and electrolyte measurements). Plasma phospholipids or red blood cell fatty acids can be monitored if the assay is available (grade of evidence: *low*).
Annual screening of all people with CF at ≥10 years of age is recommended for glucose tolerance (grade of evidence: *low*).
It is recommended that children and adolescents undergo dietary review at least every 3 mo, including questions about adherence to dietary advice (grade of evidence: *low*).
It is recommended to assess calcium intake at least annually (grade of evidence: *low*).
It is recommended to assess bone mineral density using dual-energy x-ray absorptiometry (DXA) in all people with CF from 8 to 10 years of age and then every 1 year to 5 years, depending on the age of the patient, value of the previous scan, and presence of risk factors (eg, physical inactivity, glucocorticoid therapy). For patients younger than 20 years of age whose height is more than 1 standard deviation below age- and sex-matched healthy controls bone mineral density *z* score should be adjusted for height or statural age to avoid overestimating deficits in bone mineral density in people with short stature.

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TABLE 3. Recommendations for energy requirements

Age	Energy target	Detail
Infants and children 2 years or younger	110%–200% of energy requirements for same-age healthy infants and children	Energy intake should be adapted to achieve normal weight- and length-for-age percentiles
Children 2–18 years	110%–200% of energy requirements for same-age healthy children	Energy intake should be adapted to achieve target BMI percentile tailored to 1-year age intervals

Fat-Soluble Vitamin Deficiency

Fat-soluble vitamin deficiency is common, occurring in 10% to 35% of children with pancreatic insufficiency. It is unusual, however, for people with CF to show clinical signs of overt deficiency. Instead, the goal of evaluation and treatment is to correct suboptimal levels and achieve optimal biochemical values of these vitamins.

For pancreatic insufficient patients, it is recommended to evaluate plasma levels of fat-soluble vitamins after initiation of enzyme and vitamin supplementation; 3 to 6 months after initiation or change in vitamin therapy; and annually thereafter. Vitamin supplements should be taken together with high-fat food and pancreatic enzyme supplements to improve absorption. When biochemical deficiency is detected despite adequate vitamin supplementation, poor adherence or poor absorption of supplements must be ruled out before adjusting the dosage. For pancreatic sufficient patients, it is recommended to assess vitamin sufficiency annually using plasma levels.

In recent years the adequacy of vitamin D supplementation in CF has received considerable attention. Vitamin D plays a major role in intestinal calcium absorption, and deficiency of this vitamin is one of several factors that can contribute to reduced bone mineral density in people with CF. The major source of vitamin D, exposure of skin to sunlight, can vary widely between individuals and available sunlight, which in turn depends on geographical latitude. The best indicator of vitamin D status is serum 25-hydroxy vitamin D (25[OH]D).

Vitamin D deficiency is common and has been reported in 22% of infants with CF at newborn screening; and > 90% of older children and young adults with CF were found to have suboptimal levels of 25(OH)D in 1 study. Table 5 shows the recommendations for fat-soluble vitamin supplementation.

It is suggested to supplement children with CF with vitamin D to maintain serum 25(OH)D concentrations >20 ng/mL (50 nmol/L). The supplemental dose should take into consideration dietary intake and sunlight exposure of the individual patient. Although there is some debate, vitamin D_3 is preferred over D_2 for supplementation in people with CF. Serum monitoring of 25(OH)D is recommended annually, preferably at the end of dark months, and 3 to 6 months after a dosage change.

TABLE 4. Recommendations for pancreatic enzyme replacement therapy

Age	Suggested supplementation
Infants (up to 12 months)	2000–4000 U lipase/120 mL formula or estimated breast milk intake and approximately 2000 U lipase/gram dietary fat in food
Children 1–4 years	2000–4000 U lipase/gram dietary fat, increasing dose upward as needed (maximum dose 10,000 U lipase/kg per day)
Children >4 years and adults	Consider starting at 500 U lipase/kg per meal, titrating upward to a maximal dose of: 1000–2500 U lipase/kg per meal, *or* 10,000 U lipase/kg per day, *or* 2000–4000 U lipase/gram dietary fat taken with all fat-containing meals, snacks, and drinks

Seventy-two-hour fecal fat measurement and the calculation of the coefficient of fat absorption may be used in patients whose nutritional status is questionable.

Electrolytes, Minerals, and Trace Elements

People with CF may have higher than normal requirements for salt, calcium, iron, zinc, and selenium as a consequence of the increased sweating, intestinal malabsorption, and chronic inflammation that are common in CF.

Excessive salt loss in sweat can result in inadequate levels of sodium in people with CF of all ages, and may lead to impaired growth in infants. Zinc status in people with CF has been variously reported as adequate and low. Zinc deficiency can be associated with a broad range of symptoms in CF, including growth retardation, increased susceptibility to infections, delayed sexual maturation, eye problems, and anorexia caused by reduced sense of taste (hypogeusia). Recommendations for sodium (as sodium chloride) and zinc supplementation are described in Tables 6 and 7, respectively.

NUTRITION INTERVENTION

It is recommended to base nutrition intervention on a full review of nutrition status, including a detailed review of PERT, and correction of any underlying medical conditions (grade of evidence: *high*).

It is recommended to use age-appropriate body mass index–related thresholds for deciding when to advance nutrition intervention (grade of evidence: *high*).

A progressive approach to intensification of nutrition interventions as needs increase is recommended: preventive nutritional counseling, dietary modification and/or oral nutrition supplements, and enteral tube feeding (grade of evidence: *low*).

Clinicians are recommended to consider the use of oral nutritional supplements for treating children and adults who fail to achieve optimal growth rates and nutritional status with oral dietary intake and pancreatic enzyme replacement therapy (PERT) alone (grade of evidence: low).

Recommendations for sodium (as sodium chloride) and zinc supplementation are status with oral dietary intake and PERT alone (grade of evidence: *low*).

Clinicians are recommended to consider the use of polymeric enteral tube feeding when oral interventions have failed to achieve acceptable rates of growth and nutritional status (grade of evidence: *high*).

Although additional research trials will strengthen the evidence base for many recommendations, there is a specific need for

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TABLE 5. Fat-soluble vitamin guidelines for pancreatic insufficient patients with cystic fibrosis = consensus guidelines

Vitamin	Supplementation	Serum reference values and monitoring frequency
Fat-soluble vitamins		
Vitamin A	Amounts dependent on serum values, and supplement form:	Normal reference range provided by the laboratory processing the sample
	Retinol (preformed):	
	Start low	Monitor annually and 3–6 mo after a dosage change. Also test when pregnancy is considered.
	Adapt rapidly to target normal serum reference range	
	Beta-carotene (provitamin A):	
	Prescribe 1 mg · kg^{-1} · day^{-1} (maximum 50 mg/day) for 12 wk	
	Follow with maintenance dose (maximum 10 mg/day)	
Vitamin D	Dependent on serum values, which vary with dietary intake and sun exposure:	Serum-25 (OH) D minimum 20 ng/mL (50 nmol/L)
	Starting dose of D3 (cholecalciferol)	Monitor annually, and check 3–6 months after a dosage change
	Infants 400 IU/day (advance to upper limit of 1000 IU/day)	
	All others 800 IU/day (advance to upper limit of 2000 for children 1–10 years, and 4000 IU/day for older)	
	Maintenance dose: adapt to annual serum values, preferably measured at the end of dark months	
Vitamin E (tocopherols)	α-Tocopherol dosing: 100–400 IU/day 50 IU/day for infants <12 mo (1 mg = 1.49 IU)	Plasma α-tocopherol:cholesterol ratio >5.4 mg/g; monitor annually, and check 3–6 mo after a dosage change
Vitamin K	Vitamin K_1	Routine biochemical measurement not widely available
	Infants: 0.3–1.0 mg/day	
	Older children and adults: 1–10 mg/day	
Water-soluble vitamins		
Folic acid	Women planning to become pregnant, and during first trimester of pregnancy: 400 μg/day	
Vitamin B_{12}	May need supplementation after extensive ileal resection.	
	When deficient: 100 μg/mo, intramuscular injection	
Vitamin C	Supplement only when nutritional intake is insufficient	

25(OH)D = 25-hydroxyvitamin D.

TABLE 6. Recommendations for sodium supplementation (as sodium chloride) in children with cystic fibrosis (grade of evidence: moderate)

Age	Sodium supplementation	Detail
Breast-fed infants 0–6 months	1–2 mmol · kg^{-1} · day^{-1}	For infants at risk of sodium deficiency give salt in small portions throughout the day, diluted in water or fruit juice.
For infants with special considerations (see detail, right)	Up to 4 mmol/kg/day	Increase intake for infants living in hot ambient temperatures; or for those with increased fluid loss due to vomiting, fever, diarrhea, or tachypnea; or infants with ostomies.
Older children and adolescents	Salty foods or sodium chloride capsules or vials	Supplement in stress situations when excessive sweating is expected (ie, fever, exercise/sports, hot weather).

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TABLE 7. Recommendations for zinc supplementation in children with cystic fibrosis

Age	Recommended supplementation	Recommended dosing period, mo
Infants and children younger than 2 year and at risk of zinc insufficiency	1 mg · kg^{-1} · day^{-1} (max 15 mg/day)	6
Children 2–18 years and at risk of zinc insufficiency	15 mg/day	6

studies on new treatments for nutritional complications of specific fatty acids, antiosteoporotic agents, anti-inflammatory agents, anabolic therapies, and probiotics.

CONCLUSIONS

Nutritional care and support should be an integral part of management of CF. Obtaining a normal growth pattern in infants, children, and adolescents is a major goal of multidisciplinary CF centers.

REFERENCE

1. Turck D, Braegger C, Colombo C, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with cystic fibrosis. *Clin Nutr* 2016;35:557–77.

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